DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

CBER-00-0029

August 2, 2000

Mitchel S. Berger, M.D.
Professor
Chair, Neurological Surgery
University of California, San Francisco
505 Parnassus
Room M787
San Francisco, California 94143

Dear Dr. Berger:

During the inspection ending on May 23, 2000, Lisa M. Althar and Jessica Walters Moell, investigators in the Seattle District Office of the Food and Drug Administration (FDA), reviewed your conduct of the study ———————————————————— This inspection was conducted under the FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

At the close of the inspection, a Form FDA 483 (Attachment A) was issued. This inspection revealed deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312. [21 CFR 312] These deviations include the following items:

1. Failure to retain records required by the signed investigational plan (protocol) and by federal regulations. [21 CFR 312.60 and 312.62]

a. There was no record of the correspondence between you and the sponsor, ———— concerning the conduct of the study. Documentation for the following items was missing.

i. A copy of Investigator's Brochure.

ii. Protocols agreed to and signed by you.

iii. Copies of consent forms, reviewed by the IRB, that were sent to the sponsor.

iv. A ———— Master Patient Log" form filled out with the information for the subjects at this site.

v. Letters from you to the sponsor regarding protocol violations that occurred during the study.

vi. Letters from the sponsor to you regarding protocol violations.

vii. A log documenting the sponsor's on-site monitoring visits.

viii. A log documenting telephone contacts with the sponsor.

ix. Your final report to the sponsor at the conclusion of the study.

b. There was no record for the following screening data.

i. The HIV test, Platelet count, MRI scan, and Karnofsky score results for subject number ———— could not be located.

ii. The HIV test result for subject number ———— was missing.

c. There were no written instructions for the custody of the study records after your departure from the University of Washington Medical Center. Furthermore, there was no record that you notified the sponsor when you left. In the protocol, under section —— entitled ———————— ———————————— it says, *"The Study Monitor should be notified if the investigator wishes to assign the study records to another party or move them to another location."*

2. Failure to maintain adequate and accurate case histories, including signed and dated consent forms, and failure to document that informed consent was obtained prior to participation in the study. [21CFR 312.60 and 312.62 (b)]

a. University of Washington Medical Center staff could not locate the signed and dated consent form for subject number ———— Furthermore, the date on the CRF entitled "Informed Consent" by the line "Date Patient Signed Consent" was after the start of the screening examinations (physical examination, MRI scan, and neurologic examination) for this subject. A study monitor identified the protocol deviation on a "Data Clarification Report" form with a note saying "patient verbally consented". There was no documentation of the verbal consent.

b. An initial consent form for subject number ———— reported to have been completed on the CRF entitled "Informed Consent", was missing. The subject signed and dated a revised consent form on Day 29 of their participation in the study, after having received infusions of the investigational product.

c. The consent form for Patient number ————was signed by the subject and the witness one day after initiation of testing for eligibility for inclusion into the study. The date next to the signature of the investigator was fifteen months after the date next to the signatures of the subject and the witness.

3. Failure to insure that the investigation was conducted according to the signed investigational plan (protocol). [21 CFR 312.60]

a. A study monitor noted that subject number ———— had a Prothrombin Time close to, but outside of, the upper limit of normal. The study monitor wrote "need letter to file" because the test result was "out of range" on the form entitled "Case Report Form Monitoring Notes". No further documentation could be found for this deviation from the protocol.

b. The protocol required that infusion of the investigational product stop if a subject developed a headache. However, when two subjects developed headaches during the course of their infusions, the administration of the investigational product was continued. Subsequently, both subjects had adverse events requiring hospitalization.

i. Subject numbe ———complained of headache and posterior neck pain twenty minutes after the beginning of the infusion of the investigational product. The infusion was continued for three minutes longer. After the infusion, the subject was given ——— Fever and an elevated blood pressure were also noted. He was transported to the Intensive Care Unit. A CT scan showed that the tip of the ——— ———nad penetrated through the wall of the ventricle since the time of the MRI scan, which was done prior to the infusion.

ii. Subject numbe ——— had a headache during the administration of the investigational product, and the infusion was continued. After the infusion was completed, the subject developed chills, fever, and an elevated blood pressure. The subject had a seizure, and was transported to the Intensive Care Unit.

b. The protocol required that the investigational product be injected over a period of 30 to 60 minutes.

i. According to both the CRF " ——— ——— ——— the infusion for subject number ——— lasted 19 minutes.

ii. For subject number ——— the CRF ——— ——— said that the infusion lasted 30 minutes. However, the form ——— ——— said the infusion took 20 minutes.

c. Subject numbe ——— experienced adverse events of headache and weakness, that were not listed on the CRF entitled "Adverse Events".

d. Post-therapy follow-up data for subject number ——— was missing.

Please also address the following items:

1. Did the sponsor provide any guidance on the extent of the ——— ———in order to permit the enrollment of subjects under the protocol? If so, please provide documentation.

2. Prior to surgery, was there any discussion with subjects about the degree to which their ——— to permit enrollment under the protocol? If so, please provide documentation.

3. Please provide a current copy of your curriculum vitae, including a list of all of the studies involving the use of investigational products in human subjects in which you have participated or are currently participating.

Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations for clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR 312. This commitment includes insuring that you will conduct the study in accordance with the protocol, and that you will maintain adequate and accurate records of the study. The inspection results show that you did not follow the protocol, you did not maintain complete and accurate records, and that you did not insure adequate oversight of study personnel regarding recordkeeping requirements. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. This letter is not intended to be an all inclusive list of the deficiencies with this clinical trial.

Please notify this office in writing, within 15 business days of the receipt of this letter, of the steps you have taken to correct the noted violations, as well as any steps taken to prevent the occurrence of similar violations in ongoing and future studies. If corrective action cannot be completed within 15 business days, please state the reason for the delay and the time within which the corrections will be completed.

Failure to achieve correction may result in enforcement action without further notice. These actions could include initiation of investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and the termination of an investigational new drug application (IND).

Please send your written response to:

Mary Andrich, M.D.
Office of Compliance and Biologics Quality, HFM-664
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Attachments:
Attachment A: Form FDA 483, Inspectional Observations, dated May 23, 2000.

cc: